

06/07/99
Jc672 U.S. PTO

Please type a plus sign (+) inside this box → ☐

Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. 99,501

First Inventor or Application Identifier Petersen, D.

Title Bone Graft Substitute Composition

Express Mail Label No. EG254840879US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 18]
(preferred arrangement set forth below)
 - Descriptive title of the invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the invention
 - Brief Summary of the invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 113) [Total Sheets]
4. Oath or Declaration (unexecuted) [Total Pages 3]
 - a. ☒ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

ADDRESS TO:

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment Papers (cover sheet & document(s))
8. ☒ 37 C.F.R. § 3.73(b) Statement (when there is an assignee) ☒ Power of Attorney
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
11. ☐ Preliminary Amendment
12. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. ☐ * Small Entity Statement(s) ☐ Statement filed in prior application, (PTO/SB/09-12) Status still proper and desired
14. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. ☐ Other:

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____

Prior application information: Examiner _____ Group / Art Unit: _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label

(Insert Customer No. or Attach bar code label here)

or ☒ Correspondence address below

Name	Larry W. McKenzie				
	Walker, McKenzie & Walker, P.C.				
Address	6363 Poplar Avenue, Suite 434				
City	Memphis	State	TN	Zip Code	38119-4896
Country	USA	Telephone	901-685-7428	Fax	901-682-6488

Name (Print/Type)	Larry W. McKenzie	Registration No. (Attorney/Agent)	28,239
Signature	Larry W. McKenzie	Date	6-7-99

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231.

SPECIFICATION

(3) TITLE OF THE INVENTION:

BONE GRAFT SUBSTITUTE COMPOSITION

(4) CROSS-REFERENCE TO RELATED APPLICATIONS:

Not Applicable.

(5) STATEMENT RE FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT:

Not Applicable.

(6) REFERENCE TO A "MICROFICHE APPENDIX":

Not Applicable.

(7) BACKGROUND OF THE INVENTION:

1. Field of the Invention: The present invention relates, in general, to bone graft substitute compositions.

2. Information Disclosure Statement: Calcium sulfate has been clinically used for many years as a bone void filler with successful results.

A preliminary patentability search produced the following patents which appear to be relevant to the present invention:

Hanker *et al.*, U.S. Patent 4,619,655, issued October 28, 1986, discloses an animal implant comprising a scaffold material composed of plaster of Paris and a non-

bioresorbable calcium material (such as calcium phosphate ceramic particles) bound with the plaster of Paris; a method of inserting such a composition in fluid or semisolid form into the appropriate body location of an animal (e.g., about a fracture locus); and a method of inserting a preform of such composition into the appropriate location of an animal (e.g., at the locus of a fracture).

Gitelis, U.S. Patent 5,147,403, issued September 15, 1992, discloses a method or technique for implanting a prosthesis comprising the steps of first preparing the surface of a bone to receive the prosthesis, then applying a calcium sulfate suspension in free flowing form to the prepared bone surface, and then seating the prosthesis to the coated bone surface.

Randolph, U.S. Patents 5,614,206, issued March 25, 1997, and 5,807,567, issued September 15, 1998, disclose processes for preparing pellets by mixing of calcium sulfate, water and other medicaments to provide controlled release of calcium sulfate and medicaments.

Snyder, U.S. Patent 5,425,769, issued June 20, 1995, discloses a composition for an artificial bone substitute material consisting of collagen in a calcium sulfate matrix which can be rendered porous by a foaming agent. The composition is adaptable for osseous repair by adjusting the collagen and calcium sulfate in varying ratios to suit particular applications and including admixtures of growth factors.

Sottosanti, U.S. Patent 5,366,507, discloses a composition for use in bone tissue regeneration, the composition containing a barrier material and a graft material. The barrier material can be calcium sulfate, while the graft material may consist of a composite graft material containing demineralized, freeze-dried, allogenic bone and calcium sulfate.

Sottosanti, U.S. Patent 5,569,308, discloses a method for use in bone tissue regeneration including first filling a graft site with graft material, and then placing a layer

of barrier material over at least a portion of the graft material. The barrier material can be calcium sulfate, while the graft material may consist a composite graft material containing demineralized, freeze-dried, allogenic bone and calcium sulfate.

5 Hanker *et al*, "Setting of Composite Hydroxylapatite/Plaster Implants with Blood for Bone Reconstruction," *Proceedings of the 44th Annual Meeting of the Electron Microscopy Society of America*, Copyright 1986, discloses using blood as the only moistening agent in a plaster or plaster/HA mixture as long as accelerator salts are utilized, and suggests that the putty-like consistency of such compositions offers distinct advantages in moldability and workability.

10 Osteotech, Inc., of Shrewsbury, New Jersey, markets a bone graft substitute under the mark Grafton®. It is comprised of demineralized bone matrix and glycerol as a carrier material. The carrier material, glycerol, is a viscous, gel-like, weak alcohol that is hydrophilic and water soluble. It is recognized by the Food and Drug Administration as a "Generally Regarded As Safe" substance.

15 DePuy, Inc., of Warsaw, Indiana, markets a bone graft substitute under the mark DynaGraft. It is comprised of demineralized bone matrix and poloxamer as a carrier material. Poloxamer is a reverse phase polymer which becomes more viscous with increasing temperature.

20 Nothing in the known prior art discloses or suggests the present invention. More specifically, nothing in the known prior art discloses or suggests a bone graft substitute composition including calcium sulfate, a mixing solution such as sterile water, and a plasticizing substance such as carboxymethylcellulose, and having an extended set time and sufficient robustness to withstand fluid impact with minimal erosion.

(8) BRIEF SUMMARY OF THE INVENTION:

A basic concept of the present invention is to provide bone graft substitute composition having an extended set time and sufficient robustness to withstand fluid impact with minimal erosion for expanded clinical applications.

5 The bone graft substitute composition of the present invention comprises, in general, calcium sulfate; a mixing solution such as sterile water; and a plasticizing substance such as carboxymethylcellulose.

One object of the present invention is to provide a bone graft substitute composition that can be mixed into a paste and then loaded into a syringe and ejected
10 for an extended period of time (e.g., more than ten minutes).

Another object of the present invention is to provide a bone graft substitute composition that can be mixed into a putty and then handled and formed into desired shapes for an extended period of time (e.g., more than ten minutes).

(9) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS :

Not Applicable.

(10) DETAILED DESCRIPTION OF THE INVENTION:

The bone graft substitute composition of the present invention comprises, in general, a quantity of calcium sulfate, a quantity of fluid (e.g., sterile water), and a quantity of a plasticizing substance (e.g., carboxymethylcellulose) which provides a
20 resultant composition that is robust and has an extended set time. The extended set time of the resultant composition provides a useful working time of at least 10 minutes to allow sufficient time for a surgeon to properly apply the bone graft substitute composition, while the robustness of the resultant composition allows the implanted

composition to withstand the typical pressure of body fluids, irrigation fluids and/or suctioning with minimal material erosion, disintegration or dissolution.

The bone graft substitute composition of the present invention may comprise a mixture of calcium sulfate; a mixing solution selected from the group consisting of sterile
5 water, inorganic salts, and cationic surface active agents including sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, potassium sulfate, EDTA, ammonium sulfate, ammonium acetate, and sodium acetate, etc.; and a plasticizing substance selected from the group consisting of cellulose derivatives including sodium carboxymethylcellulose, methycellulose, hydroxypropyl methylcellulose, ethylcellulose,
10 hydroxethylcellulose and cellulose acetate butyrate, and higher molecular weight alcohols including glycerol and vinyl alcohols, etc. The bone graft substitute composition may include demineralized bone matrix. One formulation of the composition may be approximately 100 parts calcium sulfate by weight, 11.1 parts carboxymethylcellulose by weight, 185.2 parts water by weight, and 69.4 parts
15 demineralized bone matrix by weight. Another formulation of the composition may be approximately 100 parts calcium sulfate by weight, 6.3 parts carboxymethylcellulose by weight, and 31 parts water by weight. Another formulation of the composition may be approximately 100 parts calcium sulfate by weight, 1.2 parts carboxymethylcellulose by weight, and 31 parts water by weight. Another formulation of the composition may be
20 approximately 80-120 parts calcium sulfate by weight, 1-40 parts carboxymethylcellulose by weight, and 21-250 parts water by weight. The composition may include a bioactive agent selected from the group consisting of demineralized bone matrix, growth factors, hyaluronic acid, bone morphogenic proteins, bone autograft, and bone marrow, etc. The composition may include sodium bicarbonate. For example, the
25 composition may include 0.1-2% sodium bicarbonate by weight for creating a porous

structure in the resultant composition. Possible embodiments of the bone graft substitute composition of the present invention may include at least one additive selected from the group consisting of antiviral agent, antimicrobial agent, antibiotic agent, amino acid, peptide, vitamin, inorganic element, protein synthesis co-factor, hormone, endocrine tissue, synthesizer, enzyme, polymer cell scaffolding agent with parenchymal cells, angiogenic drug, demineralized bone powder, collagen lattice, antigenic agent, cytoskeletal agent, mesenchymal stem cells, bone digester, antitumor agent, cellular attractant, fibronectin, growth hormone, cellular attachment agent, immunosuppressant, nucleic acid, surface active agent, hydroxyapatite, penetration enhancer, bone allograft, and chunks, shards, and/or pellets of calcium sulfate.

Preferred Embodiment 1:

An injectable bone graft substitute composition having the following preferred formulation: 100 parts by weight of medical grade calcium sulfate hemihydrate (MGCSH), 11.1 parts by weight of carboxymethylcellulose (CMC), 69.4 parts by weight of demineralized bone matrix (DBM), and 162 parts by weight of sterile water.

The preferred method for mixing this putty bone graft substitute composition comprises the following steps: (1) dry blend the powder components (i.e., the calcium sulfate hemihydrate, carboxymethylcellulose, and demineralized bone matrix); (2) add the sterile water; and (3) mix or stir all components for approximately 30 seconds to one minute or until the desired putty-like consistency is achieved.

The resultant injectable bone graft substitute composition has the following characteristic/criteria:

Handability — the resultant composition should: (a) be a single cohesive bolus; (b) be able to be handled and manipulated with minimal to no material transfer

(sticking) to latex gloved hand; (c) be able to be handled without material crumbling or falling apart; and (d) exhibit minimal cracking or “tearing” with extreme manipulation, e.g., hard squeezing;

Ejectability — the resultant composition should: (a) be able to be easily manipulated, e.g., rolled into a long cylinder or other suitable shape, so as to be manually placed into an appropriate injection apparatus, e.g., a syringe; and (b) be able to be ejected through a 1/8 inch (0.3175 centimeter) diameter orifice with relatively little pressure required; and

Robustness — the resultant composition, after being placed or injected into or onto the desired location, should be able to withstand body fluids, reasonable irrigation fluids and/or suctioning with minimal material erosion, disintegration or dissolution.

Preferred Embodiment 2:

A putty bone graft substitute composition having the following preferred formulation: 100 parts by weight of medical grade calcium sulfate hemihydrate (MGCSH), 6.3 parts by weight of carboxymethylcellulose (CMC), and 31 parts by weight of sterile water.

The preferred method for mixing this putty bone graft substitute composition comprises the following steps: (1) dry blend the powder components (i.e., the calcium sulfate hemihydrate, and carboxymethylcellulose); (2) add the sterile water; and (3) mix or stir all components for approximately 30 seconds to one minute or until the desired putty-like consistency is achieved.

The resultant putty bone graft substitute composition has the following characteristic/criteria:

Handability — the resultant composition should: (a) be a single cohesive bolus; (b) be able to be handled and manipulated with minimal to no material transfer (sticking) to latex gloved hand; (c) be able to be handled without material crumbling or falling apart; and (d) exhibit minimal cracking or “tearing” with extreme manipulation, e.g., hard squeezing; and

Robustness — the resultant composition, after being placed or injected into or onto the desired location, should be able to withstand body fluids, reasonable irrigation fluids and/or suctioning with minimal material erosion, disintegration or dissolution.

Preferred Embodiment 3:

A paste bone graft substitute composition having the following preferred formulation: 100 parts by weight of medical grade calcium sulfate hemihydrate (MGCSH), 1.2 parts by weight of carboxymethylcellulose (CMC), and 31 parts by weight of sterile water.

The preferred method for mixing this putty bone graft substitute composition comprises the following steps: (1) dry blend the powder components (i.e., the calcium sulfate hemihydrate, and carboxymethylcellulose); (2) add the sterile water; and (3) mix or stir all components for approximately 30 seconds to one minute or until the desired putty-like consistency is achieved.

The resultant paste bone graft substitute composition has the following characteristic/criteria:

Ejectability — the resultant composition should be able to be ejected through a 1/8 inch (0.3175 centimeter) diameter orifice with relatively little pressure required.

Preferred Embodiment 4:

A bone graft substitute composition having the following preferred formulation:
approximately 80-120 parts medical grade calcium sulfate hemihydrate by weight;
approximately 21-250 parts sterile water by weight; and approximately 1-40 parts
5 sodium carboxymethylcellulose by weight. This preferred formulation may include
approximately 10-100 parts demineralized bone matrix by weight.

The preferred method for mixing this bone graft substitute composition comprises
the following steps: (1) dry blend the powder components (i.e., the calcium sulfate
hemihydrate, and sodium carboxymethylcellulose, and, if included, the demineralized
bone matrix); (2) add the sterile water; and (3) mix or stir all components for
approximately 30 seconds to one minute or until the desired consistency is achieved.

The resultant bone graft substitute composition has the following
characteristic/criteria:

Handability — the resultant composition should: (a) be a single cohesive
bolus; (b) be able to be handled and manipulated with minimal to no material transfer
(sticking) to latex gloved hand; (c) be able to be handled without material crumbling or
falling apart; and (d) exhibit minimal cracking or “tearing” with extreme manipulation,
e.g., hard squeezing;

Ejectability — the resultant composition should: (a) be able to be easily
manipulated, e.g., rolled into a long cylinder or other suitable shape, so as to be manually
placed into an appropriate injection apparatus, e.g., a syringe; and (b) be able to be
ejected through a 1/8 inch (0.3175 centimeter) diameter orifice with relatively little
pressure required; and

Robustness — the resultant composition, after being placed or injected

into or onto the desired location, should be able to withstand body fluids, reasonable irrigation fluids and/or suctioning with minimal material erosion, disintegration or dissolution.

Tests:

- 5 The majority of tests done to date on the bone graft substitute composition of the present invention basically consist of mixing a specific formulation and then assessing and recording the mixing, handling, consistency, and injectability properties of the resultant material.

Formulation Tests:

Injectable Bone Graft Substitute Composition: Formulations with various types and amounts of carboxymethylcellulose and demineralized bone matrix have been tested. Specific examples include: (1) carboxymethylcellulose percentages of 1-10% by weight; (2) types of carboxymethylcellulose have included high viscosity, medium viscosity, and low viscosity from 3 vendors (e.g., Aqualon® 7HF PH sodium carboxymethylcellulose from Hercules Incorporated, Hercules Plaza, 1313 North Market Street, Wilmington, DE 19894-0001); (3) carboxymethylcellulose sterilized by gamma or electronic beam sterilization (medium and low doses); (4) demineralized bone matrix percentages up to 65% by volume; (5) differently processed demineralized bone matrix, air dried and freeze dried; (6) demineralized bone matrix from two vendors (e.g., human freeze dried demineralized bone matrix from AlloSource, 8085 E. Harvard Ave., Denver, CO 80231); and (7) animal demineralized bone matrix, including bovine and canine.

For all these formulations, varying amounts of water, between 31-200 parts by weight, have been tested. The mixing, handling, consistency, and injectability properties

were assessed and formulas chosen such that they met the mixing, handability, ejectability, and robustness characteristics/criteria stated hereinabove.

Paste And Putty Bone Graft Substitute Composition: These were the first tests done and included formulations with compositions having 100 parts by weight medical grade calcium sulfate hemihydrate, and between 1-10% by weight carboxymethylcellulose, and between 31-200 parts by weight water. As was the case with the injectable bone graft substitute composition, mixing, handability, consistency, injectability, and robustness properties were assessed for the different formulations. Specific tests have included: (1) varying the carboxymethylcellulose percentages from 0.25 % up to 10% by weight, (2) using inorganic salt solutions including 2% sodium chloride (NaCl) by weight, 2-4% sodium sulfate (Na_2SO_4) by weight, and 2% potassium chloride (KCl) by weight.

As with the injectable bone graft substitute composition, varying amounts of water, 31-200 parts by weight, were used.

Example 1:

The osteoinductive properties of the injectable bone graft substitute composition have been studied using an athymic mouse-intramuscular implantation model. This animal model is widely accepted as the “gold standard” for assessing osteoinductive characteristics of bone graft materials. In this model, a given amount of material is surgically placed into a muscular site. After an implantation period of four weeks, the osteoinductive response is assessed using various analytical methods, including radiography, biochemical analysis (alkaline phosphatase levels and calcium content), and histomorphometry.

In this study, four athymic (nude) male mice (Harlan Sprague Dawley, Inc.) were used for each material group. Two muscle pouches were formed in the right and left gluteal muscles of each mouse and implanted with either: 1) pellets which were manufactured using the composition given in Preferred Embodiment 1, or 2) twenty (20) mg of demineralized bone matrix which had been rehydrated with isotonic saline (0.9% NaCl). The pellets made from Preferred Embodiment 1 were 3.0 mm in diameter, 2.5 mm in height and 25 mg in weight.

After twenty-eight (28) days the animals were sacrificed and the materials explanted. The explants were analyzed for osteoinductive potential by assessing the alkaline phosphatase activity and for new bone growth by histomorphometric analysis of histologic sections.

Samples to be analyzed for alkaline phosphatase activity were minced, sonicated, and extracted with water saturated butanol. The extracts were assayed for protein content using a Pierce BCA Protein Assay Kit (Pierce Chemical Co.) and measuring the conversion of para-nitrophenylphosphate (pNPP) to para-nitrophenol (pNP) with time. The results were expressed as umole pNP formed/min/ug tissue protein.

Samples intended for histomorphometric analyses were prepared using standard histological procedures. The percent viable bone (new bone formation) was quantitated employing computer software (Adobe Photo Shop 3.0.4 and HNIH 1.61), in conjunction with a microscope equipped with a video camera. Data was reported as percent viable bone relative to the total cross-sectional area analyzed.

The alkaline phosphatase levels (umole pNP formed/min/ug tissue protein) and percent viable bone results for the groups of mice implanted with DBM only and with injectable putty manufactured using the composition given in Preferred Embodiment 1 are shown in Table 1.

Table 1 - Osteoinductive Results

Alkaline Phosphatase Levels and Percent Viable Bone

Group	Alkaline Phosphatase Levels (umole pNP formed/min/ug tissue protein)	Percent Viable Bone (%)
DMB only	$2.1 \times 10^{-5} \pm 0.3 \times 10^{-5}$	$6.5 \pm 1.0\%$
Injectable Putty (Preferred Embodiment 1)	$3.0 \times 10^{-5} \pm 0.2 \times 10^{-5}$	$4.7 \pm 0.9\%$

Example 2:

A study was performed on canines to evaluate healing of bone defects using materials with the composition given in Preferred Embodiment 1. The DBM used in these compositions was fresh frozen canine DBM (Veterinarian Transplant Services, Seattle, WA). Two methods were used to produce the test materials. The first material group consisted of a blend of DBM, calcium sulfate, and CMC powder that was irradiated sterilized, while the second group mixed canine DBM with the calcium sulfate-CMC blend at the time of surgery.

In this canine animal model, large medullary cylindrical defects (13 mm diameter x 50 mm length) were created bilaterally in the proximal humeri by drilling axially through the greater tubercle. Six to 7 cc of test material were injected into prepared cavities using a large-bore catheter-tip syringe. Left humeri received the premixed material that had been sterilized and the right humeri received the material mixed intraoperatively which utilized non-irradiated canine DBM. Radiographs of the humeri were obtained preoperative, immediately postoperative, and at 2, 3, and 6 weeks. Following euthanasia after 6 weeks, the explanted humeri were sectioned transversely, radiographed, and processed for plastic imbedded undecalcified histology. The histologic sections were

stained with basic fuchsin and toluidine blue and examined by light microscopy.

Post-operative radiographs revealed all test materials to be well contained in the prepared cavities. Normal wound healing occurred and there were no postoperative infections. Serial clinical radiographs showed a progressive decrease in materials density with time. no difference was evident between the right and left sides.

Contact radiographs of the cut sections demonstrated no difference in pattern or density of bone filling the right and left defects, non-irradiated and irradiated canine DBM materials groups, respectively. Serial sections for all the dogs showed between 30-100% filling of the defect, with one dog showing almost complete filling for all sections.

Histologically, the nature of new bone formation and the amount of residual material were similar in the right and left defects. In the peripheral one-third of the defects, new bone was present at the margins and haversian surfaces of abundant DBM particles. Residual calcium sulfate was evident, incorporated within slender bone trabeculae, independent of DBM particles. New bone formation in the central aspect of the defects was more variable, with some vascular fibrous tissue shown. No foreign body or inflammatory response was seen in any of the slides, indicating that the materials had extremely good biocompatibility.

Thus, materials with compositions given in Preferred Embodiment 1 were shown to be well tolerated by the bone and to heal a large medullary defect 30-100% at six weeks with viable new bone in a canine bone defect model.

Although the present invention has been described and illustrated with respect to preferred embodiments and preferred uses therefor, it is not to be so limited since modifications and changes can be made therein which are within the full intended scope of the invention.

(11) CLAIM OR CLAIMS:

1 1. A bone graft substitute composition comprising:

2 (a) calcium sulfate;

3 (b) a mixing solution selected from the group consisting of sterile water, inorganic
4 salts, and cationic surface active agents including sodium chloride, phosphate buffered
5 saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and
6 sodium acetate; and

7 (c) a plasticizing substance selected from the group consisting of cellulose
8 derivatives including sodium carboxymethylcellulose, methylcellulose, hydroxypropyl
9 methylcellulose, ethylcellulose, hydroxethylcellulose and cellulose acetate butyrate, and
10 higher molecular weight alcohols including glycerol and vinyl alcohols.

11 2. The bone graft substitute composition of claim 1 in which is included
12 demineralized bone matrix.

13 3. The bone graft substitute composition of claim 2 in which said composition is
14 approximately 40% demineralized bone matrix by dry weight.

15 4. The bone graft substitute composition of claim 2 in which said composition is
16 approximately 100 parts calcium sulfate by weight, 11.1 parts carboxymethylcellulose by
17 weight, 162 parts water by weight, and 69.4 parts demineralized bone matrix by weight.

18 5. The bone graft substitute composition of claim 1 in which said composition is
19 approximately 100 parts calcium sulfate by weight, 6.3 parts carboxymethylcellulose by

3 weight, and 31 parts water by weight.

1 6. The bone graft substitute composition of claim 1 in which said composition is
2 approximately 100 parts calcium sulfate by weight, 1.2 parts carboxymethylcellulose by
3 weight, and 31 parts water by weight.

1 7. The bone graft substitute composition of claim 1 in which said composition is
2 approximately 80-120 parts calcium sulfate by weight, 1-40 parts
3 carboxymethylcellulose by weight, and 21-250 parts water by weight.

1 8. The bone graft substitute composition of claim 1 in which is included a
2 bioactive agent selected from the group consisting of demineralized bone matrix, growth
3 factors, hyaluronic acid, bone morphogenic proteins, bone autograft, therapeutic agents,
4 analgesics, and bone marrow, bone allograft, and parenchymal and mesenchymal cells.

1 9. The bone graft substitute composition of claim 1 in which is included sodium
2 bicarbonate.

1 10. A bone graft substitute composition comprising:
2 (a) calcium sulfate;
3 (b) a mixing solution; and
4 (c) a plasticizing substance for extending the set time of the resultant composition
5 and for providing the resultant composition with sufficient robustness to withstand fluid
6 impact with minimal erosion.

- 1 11. A bone graft substitute composition comprising:
- 2 (a) approximately 80-120 parts medical grade calcium sulfate hemihydrate by
- 3 weight;
- 4 (b) approximately 21-250 parts sterile water by weight; and
- 5 (c) approximately 1-40 parts sodium carboxymethylcellulose by weight.

- 1 12. The bone graft substitute of claim 11 in which is included approximately 10-
- 2 100 parts demineralized bone matrix by weight.

(12) ABSTRACT OF THE DISCLOSURE:

A bone graft substitute composition comprising calcium sulfate; a mixing solution selected from the group consisting of sterile water, sodium chloride, phosphate buffered saline, potassium chloride, and sodium sulfate; and a plasticizing substance selected from
5 the group consisting of carboxymethylcellulose, polyvinyl alcohol, methycellulose, and hydroxypropyl methylcellulose.

Please type a plus sign (+) inside this box → ☐

PTO/SB/01 (12-97)

Approved for use through 9/30/00. OMB 0651-0032

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	99,501
	First Named Inventor	Petersen, D.
	COMPLETE IF KNOWN	
	Application Number	/
	Filing Date	
	Group Art Unit	
<input checked="" type="checkbox"/> Declaration Submitted with Initial Filing	OR	<input type="checkbox"/> Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)
Examiner Name		

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

BONE GRAFT SUBSTITUTE COMPOSITION

the specification of which (Title of the Invention)

☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) as United States Application Number or PCT International Application Number and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

[Page 1 of 2] 3

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → +

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

☐ Customer Number

OR

☒ Registered practitioner(s) name/registration number listed below

Place Customer
Number Bar Code
Label here

Name	Registration Number	Name	Registration Number
Larry W. McKenzie	28,239		
Russell H. Walker	35,401		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label

OR ☒ Correspondence address below

Name	Larry W. McKenzie				
Address	Walker, McKenzie & Walker, P.C.				
Address	6363 Poplar Avenue, Suite 434				
City	Memphis	State	TN	ZIP	38119-4896
Country	USA	Telephone	901-685-7428	Fax	901-682-6488

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Donald W.	Petersen

Inventor's Signature					Date		
Residence: City	Lakeland	State	TN	Country	USA	Citizenship	USA
Post Office Address							
Post Office Address	9700 Wood Green Lane						
City	Lakeland	State	TN	ZIP	38002	Country	USA

☒ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Please type a plus sign (+) inside this box → +

PTO/SB/02A (3-97)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.



DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Page 3 of 3

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Warren O.				Haggard			
Inventor's Signature					Date		
Residence: City		Bartlett	State	TN	Country		USA
Post Office Address							
Post Office Address		6600 Stephan Ridge Drive					
City		Bartlett	State	TN	ZIP		38134
				Country		USA	
Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Donald A.				Randolph			
Inventor's Signature					Date		
Residence: City		Wheaton	State	IL	Country		USA
Post Office Address							
Post Office Address		1605 South Prospect Street					
City		Wheaton	State	IL	ZIP		60187
				Country		USA	
Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A petition has been filed for this unsigned inventor			
Given Name (first and middle [if any])				Family Name or Surname			
Cary P.				Hagan			
Inventor's Signature					Date		
Residence: City		Germantown	State	TN	Country		USA
Post Office Address							
Post Office Address		8517 Farmington Cove					
City		Germantown	State	TN	ZIP		38139
				Country		USA	

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.



Re: Patent Application

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Donald W. Petersen, Warren O. Haggard, Donald A.
Randolph and Cary P. Hagan

For: BONE GRAFT SUBSTITUTE COMPOSITION

Docket No.: 99,501

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

POWER OF ATTORNEY AND
CERTIFICATE UNDER 37 C.F.R. § 3.73(b)

The undersigned, assignee of the entire interest in and to an application of Donald W. Petersen, Warren O. Haggard, Donald A. Randolph and Cary P. Hagan for U.S. Letters Patent for a BONE GRAFT SUBSTITUTE COMPOSITION, executed as of the _____ day of _____, 1999, and further identified by Docket No. 99,501, hereby appoints the following attorneys to prosecute this application and transact all business in the Patent and Trademark Office in connection therewith:

Larry W. McKenzie	Russell H. Walker
Registration No. 28,239	Registration No. 35,401

Send correspondence to:

Walker, McKenzie & Walker, P.C.
6363 Poplar Ave., Suite 434
Memphis, Tennessee 38119-4896

Direct telephone calls to Larry W. McKenzie at (901) 685-7428.

The below-identified Assignee certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of an Assignment from the Inventor(s), a copy of which is attached hereto.

1 The undersigned has reviewed all the documents in the chain of title of the
2 patent application identified above and, to the best of the undersigned's knowledge
3 and belief, title is in the Assignee identified below.

4 The undersigned (whose title is supplied below) is empowered to sign this
5 certificate on behalf of the Assignee.

6 I hereby declare that all statements made herein of my own knowledge are
7 true, and that all statements made on information and belief are believed to be true;
8 and further, that these statements are made with the knowledge that willful false
9 statements, and the like so made, are punishable by fine or imprisonment, or both,
10 under Section 1001, Title 18 of the United States Code, and that such willful false
11 statements may jeopardize the validity of the application or any patent issuing
12 thereon.

13 WRIGHT MEDICAL TECHNOLOGY, INC.,
14 Assignee

15 Date: _____

By: _____

16 Jason P. Hood
17 Assistant Secretary
18